IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Pittenger, et al.
Serial No.:	09/319,521
Filed:	June 4, 1999
For:	Improved Chondrogenic Differentiation of Human Mesenchymal Stem Cells
Group:	1644
Examiner:	Decloux

Commissioner for Patents
Box 1450
Alexandria, VA 22313-1450

SIR:

In response to the Final Rejection dated April 22, 2003, reconsideration of the above-identified application is hereby respectfully requested.

Claims 60-79 stand rejected under 35 U.S.C. 102(e) as being anticipated by Johnstone, et al., as evidenced by www.voigtglobal.com/Cellgro_basal_liquid.htm. This rejection is respectfully traversed.

The Federal Circuit has held that anticipation is established only if all elements of an invention, as stated in a patent claim, are identically set forth in a single prior art reference. All of the limitations must be disclosed by the reference either expressly or inherently. (*See Mehl/Biophile International Corp. v. Milgraum*, 192 F.3d 1362 (Fed. Cir. 1999) at 1365; 52 U.S.P.Q.2d 1303, at 1306; *Oney v. Ratliff*, 182 F.3d 893 (Fed. Cir. 1999); 51 U.S.P.Q.2d 1697; *Finnigan Corp. v. U.S. International Trade Commission*, 180 F.3d 1354 (Fed. Cir. 1999), at 1367; 51 U.S.P.Q.2d 1001, at 1009; *General Electric Co. v. Nintendo Co., Ltd.*, 179 F.3d 1350 (Fed. Cir. 1999), at 1356, 50 U.S.P.Q.2d 1910, at 1915.) Anticipation is a question of fact. (*Rockwell International Corp. v. United States*, 147 F.3d 1358 (Fed. Cir. 1998), at 1363; 47 U.S.P.Q.2d 1027, at 1031.)

Johnstone does not disclose or even remotely suggest to one of ordinary skill in the art a chondrogenic medium that includes a simple sugar in an amount of from about 3g/l to about 7g/l. The only specific concentration of glucose disclosed by Johnstone is 1g/l, which is in a medium known as Dulbecco's Modified Eagle's Medium-Low Glucose (DMEM-LG). Although, at Column 4, lines 31 and 32, Johnstone lists "Dulbecco's Modified Eagle's Medium (DMEM)," as an example of a medium which may be used to promote chondrogenesis of mesenchymal stem cells, DMEM does not inherently have a simple sugar concentration of from 3g/l to 7g/l. In fact, Johnstone discloses, and Examiner even admits at Page 3, lines 1-4 of the Final Rejection, that there are examples of DMEM that have a glucose concentration of only 1g/l, including the DMEM used specifically by Johnstone. Therefore, all of the limitations of Claims 60-79 are not disclosed, either expressly or inherently, by Johnstone.

In fact, contrary to the requirements for anticipation under 35 U.S.C. 102, the Examiner relies on an additional reference, the Cellgro web page, in order to formulate the rejection. Cellgro, however, adds nothing to Johnstone. Cellgro discloses various formulations of DMEM. Although some of the formulations contain 4.5g/l of glucose, one of the formulations disclosed on the Cellgro web page contains 1g/l of glucose. Thus, in view of the formulations disclosed by Cellgro, DMEM does not include inherently a simple sugar in an amount of from about 3g/l to about 7g/l.

Furthermore, Cellgro does not provide any suggestion to one of ordinary skill in the art as to the types of cells which may be cultured in DMEM including 4.5g/ml of glucose, or that DMEM including 4.5g/ml of glucose may be employed in a medium for culturing mesenchymal stem cells in order to enable the mesenchymal stem cells to differentiate into chondrocytes.

Thus, even the combination of Johnstone and Cellgro does not disclose all of the elements of Applicants' Claims 60-79, either expressly or inherently. In addition, the combination of Johnstone and Cellgro does not even remotely suggest to one of ordinary skill in the art that a culture medium having a simple sugar concentration from 3g/l to 7g/l may be used as part of a culture medium for mesenchymal stem cells for enabling the mesenchymal stem cells to differentiate into chondrocytes. Therefore, Johnstone does not anticipate Applicants' processes as claimed, nor does Johnstone render Applicants' processes as claimed obvious to one

of ordinary skill in the art. It is therefore respectfully requested that the rejection under 35 U.S.C. 102(e) be reconsidered and withdrawn.

Claims 60-99 stand rejected under 35 U.S.C. 103 as being unpatentable over Johnstone, et al. in view of Hunziker. This rejection is respectfully traversed.

The differences between Johnstone and Applicants' claimed processes have been noted hereinabove. Johnstone clearly does not disclose or even remotely suggest Applicants' claimed processes to one of ordinary skill in the art.

The Examiner relies on Hunziker to show that TGF-β3 may be used in a composition for transforming repair cells into chondrocytes. Hunziker discloses the treatment and repair of defects or lesions in cartilage by filling the defect or lesion with a biodegradable matrix containing a proliferation agent, a transforming agent, and repair cells. TGF-β, including TGF-β3, may be used as a proliferation agent and/or as a transforming factor. Insulin-like growth factor also may be used as a proliferation agent.

The composition of Hunziker, however, does not include a chemically defined minimal essential medium, ascorbate or an analog thereof, an iron source, and a simple sugar present in an amount of from 3g/l to 7g/l. Hunziker also does not even remotely suggest to one of ordinary skill in the art to include such components. Hunziker, therefore, does not disclose or even remotely suggest to one of ordinary skill in the art Applicants' processes as claimed. Thus, Hunziker does not render Applicants' processes as claimed obvious to one of ordinary skill in the art.

The combination of Johnstone and Hunziker does not disclose or even remotely suggest to one of ordinary skill in the art a process for producing mesenchymal stem cells wherein the mesenchymal stem cells are cultured in a medium which includes all of the components claimed by Applicants, including a simple sugar which is present in the medium in an amount of from 3g/l to 7g/l. Applicants and only Applicants have discovered that by culturing mesenchymal stem cells in a chondrogenic medium which includes a simple sugar at a concentration of from about 3g/l to about 7g/l, one obtains improved differentiation of mesenchymal stem cells into

chondrocytes as opposed to media which have a lower sugar concentration, such as, for example, media which have a glucose concentration which is the standard concentration present in "low glucose DMEM" (1g/l). At best, the combination of Johnstone and Hunziker would suggest to one of ordinary skill in the art to supply a chondrogenic medium which includes glucose at a concentration of only 1g/l. Johnstone and Hunziker, therefore, did not contemplate Applicants' improvement for producing chondrocytes from mesenchymal stem cells wherein there is included in the chondrogenic medium a simple sugar which is present in the medium in an amount of from about 3g/l to about 7g/l. Therefore, the combination of Johnstone and Hunziker does not render Applicants' process as claimed obvious to one of ordinary skill in the art, and it is therefore respectfully requested that the rejection under 35 U.S.C. 103 be reconsidered and withdrawn.

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejections be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,

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